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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,299	FERRARA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-25* is/are pending in the application.

4a) Of the above claim(s) *13-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7, 9-10 and 12* is/are rejected.

7)☒ Claim(s) *6,8 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4, and 6-25 are pending.

2. Claims 13-25 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

3. Claims 1-4, and 6-12, drawn to polypeptide, are being acted upon in this Office Action.

4. In view of the amendment filed 1/12/06, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 7, 9-10 and 12 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human endocrine gland-derived vascular endothelial growth factor (EG-VEGF) for screening assays, (2) an isolated polypeptide comprising amino acid residues 20 to 105 of SEQ ID NO: 2 wherein the polypeptide is a mature EG-VEGF, **does not** reasonably provide enablement for (1) any isolated polypeptide comprising "an amino acid sequence" having at least "about 80%, 85%, 90%, or 95% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) the isolated polypeptide comprising "an amino acid sequence" having at least "about 80% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is a native sequence of endocrine gland-derived vascular endothelial growth factor (EG-VEGF), (3) the isolated polypeptide comprising "an amino acid sequence" having "at least about 80% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is any "allelic variant" of EG-VEGF, and (4) the isolated polypeptide comprising "an amino acid sequence" having at least "about 80% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the native polypeptide is human for treating any diseases. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompass any polypeptide that comprise the full-length sequence having at least about 80%, 85%, 90%, or 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or any polypeptide that comprise an amino acid sequence having at least about 80%, 85%, 90%, 95% identity to any portion of amino acid residues 20-105 of SEQ ID NO: 2.

The term "EG-VEGF variant polypeptide" as defined in the specification at page 13 is any EG-VEGF having one or more amino acid residues are added, or deleted, tat the N- and/or C-terminus as well as within one or more internal domains of SEQ ID NO: 2. The EB-VEGF variant polypeptide does not encompass the native EG-VEGF polypeptide sequence. EG-VEGF variant polypeptides are at least 10 amino acids in length (see page 14). The allelic variant of EG-VEGF will have at least about 80%, 85%, 90% or 95% identity from x to 105 of amino acid of SEQ ID NO: 2 (see page14).

The specification discloses only one isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human EG-VEGF for screening agonist or antagonist (page 54-56) and production of antibody that binds specifically to EG-VEGF (See page 65). The mature protein is from residues 20 to 105 of SEQ ID NO: 2. The specification further discloses that EG-VEGF is expressed in the endocrine tissues such as the stroma cell and granulose cells in the ovary, the Leydig cell in the testis, the adrenal gland and the placenta. The EG-VEGF is mitogenic and chemo attractant for specific endothelial cells but not human aortic vascular smooth muscle cells, pericytes, fibroblast, human neonatal fibroblasts and karatinocytes. The angiogenic effect of EG-VEGF is tissue specific since EG-VEGF has no effect on rat corneal pocket assay. The specification further discloses that injection of Adenoviral vector carrying the

human EG-VEGF cDNA or VEGF causes an increase in angiogenesis, large fluid-filled or hemorrhagic cystic formation in ovary (Fig. 19).

The specification does not teach how to identify other EG-VEGF polypeptide or variants thereof that has at least about 20%, 15%, 10% or 5% amino acids difference, much less which undisclosed EG-polypeptide is effective for treating any diseases. The term "about" expands the percentage identity to either or both ends of 80%, 85%, 90% and 95%. Further, the term "an amino acid sequence" could be any portion of residues 20 to 105 of SEQ ID NO: 20 and having at least about 80%, 85%, 90% or 95% identity to said portion. The specification does not teach which amino acids within the full-length sequence of SEQ ID NO: 2 are critical and can or cannot be change such as substitution, deletion, addition and combination thereof and whether the resulting polypeptide maintains its structure and function, in turn, useful for treating which disease. Based on the definition of variants, the EG-VEGF polypeptide having one *or more* amino acid residues are added, or deleted, at the N- and/or C-terminus as well as *within one or more internal domains* of SEQ ID NO: 2 would have no resemblance to residues 20 to 105 of SEQ ID NO: 2. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. Without the amino acid sequence, one of skill in the art cannot make, much less use the claimed polypeptide.

Further, the use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because of the lack of disclosure about any polypeptide comprising any amino acid sequence having at least about 80%, 85%, 90%, 95% sequence identity to any portion from 20, 21, 22... to 105 of SEQ ID NO: 2, including any "allelic variants" of SEQ ID NO: 2, it is unpredictable which undisclosed polypeptide has which function, in turn, would be useful for treating which all diseases in the absence of in vivo working example. Assuming the undisclosed polypeptide still binds to its receptor and promotes proliferation, what disease could be treated without having the concern of cancer formation, especially the EG-VEGF polypeptide has angiogenic property.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495; PTO 1449). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al*, PTO 1449, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular).

Attwood *et al*, PTO 1449, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Skolnick *et al*, PTO 1449, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Further, there is a lack of in vivo working example demonstrating the claimed polypeptide could treat *any* disease for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the *blood testicular barrier* or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Fogarty *et al*, PTO 1449, teach targeting angiogenesis using VEGF antagonist is a promising anticancer approach, however, the twelve recent failures in clinical trials using VEGF antagonist, indicate the unpredictability of angiogenesis inhibitors for cancer treatment. Although the specification suggests that EG-VEGF, like VEGF, may be a potential cause of polycystic

ovary syndrome (See Fig 19, in particular), no showing of the cause and effect has been demonstrated.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/12/06 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended to recite a single reference sequence. Amino acid residues 20 to 105 of SEQ ID NO: 2 correspond to a mature form of EG-VEGF, see page 10, lines 20-21, page 79, lines 6-14, and Figure 16A. One of skill in the art would have been able to identify EG-VEGF variants without undue experimentation using the EST techniques, hybridization probes, or anti-EG-VEGF as described in the specification. Enclosed post filing date references LeCouter et al (2003, Endocrinology 144: 2606-2616) uses EST high to identify mouse EG-VEGF has 88% identity to amino acid residues 20-105 of SEQ ID NO: 2 (see Figures 1B and 7A in LeCouter et al). Masuda et al identified rat EG-VEGF, which has approximately 91% identity with amino acid residues 20-105 of SEQ ID NO: 2. Kisliouk et al identified bovine EG-VEGF which has approximately 88% identity with amino acid residues 20-105 of SEQ ID NO: 2, see Table 1. With regard to the term "comprising" the specification discloses that EG-VEGF can have a signal sequence, full-length EG-VEGF (SEQ ID NO: 2), chimeric molecule comprising EG-VEGF, such as EG-VEGF can be fused with epitope tag, poly-his tag (see page 35, line 13 to page 36, line 11).

In response, the amended claims encompass any polypeptide that comprise the full-length sequence having at least about 80%, 85%, 90%, 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or any polypeptide that comprise an amino acid sequence having at least about 80%, 85%, 90%, 95% identity to any portion of amino acid residues 20-105 of SEQ ID NO: 2. This is because polypeptide comprising "*an* amino acids sequence" is limited to the amino acid

residues 20 to 105 of SEQ ID NO: 2. Further, the term "a amino acid sequence" could be any polypeptide having at least about 80%, 85%, 90% or 95% identity to any portion of amino acid residues 20 to 105 of SEQ ID NO: 2. The specification does not teach how to identify other EG-VEGF polypeptide or variants thereof that has at least about 20%, 15%, 10% or 5% amino acids difference, much less which undisclosed EG-polypeptide is effective for treating any diseases. The term "about" expands the percentage identity to either or both ends of 80%, 85%, 90% and 95%. The specification does not teach which amino acids within the full-length sequence of SEQ ID NO: 2 are critical and can or cannot be change such as substitution, deletion, addition and combination thereof and whether the resulting polypeptide maintains its structure and function, in turn, useful for treating which disease. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. Without the amino acid sequence, one of skill in the art cannot make, much less use the claimed polypeptide. As such, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In response to the argument that the specification discloses EG-VEGF can have a signal sequence, full-length EG-VEGF (SEQ ID NO: 2), or chimeric molecule comprising EG-VEGF, such as EG-VEGF can be fused with epitope tag, poly-his tag, amending the claims to recite a chimeric protein comprising the amino acid residues 20 to 105 of SEQ ID NO: 2 fused to a heterologous polypeptide selected from the group consisting of the ones recited at page 35 lines 24-30 would obviate this rejection.

7. Claims 1-4, 7, 9-10 and 12 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated polypeptide comprising "an amino acid sequence" having at least "about 80%, 85%, 90%, or 95% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) the isolated polypeptide comprising "an amino acid sequence" having at least "about 80% identity" to amino acid residues

20 to 105 of SEQ ID NO: 2, wherein the polypeptide is a native sequence of endocrine gland-derived vascular endothelial growth factor (EG-VEGF), (3) the isolated polypeptide comprising "an amino acid sequence" having "at least about 80% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is any "allelic variant" of EG-VEGF, and (4) the isolated polypeptide comprising "an amino acid sequence" having at least "about 80% identity" to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the native polypeptide is human for treating any diseases.

The claims encompass any polypeptide that comprise the full-length sequence having at least about 80%, 85%, 90%, 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or any polypeptide that comprise an amino acid sequence having at least about 80%, 85%, 90%, 95% identity to any portion of amino acid residues 20-105 of SEQ ID NO: 2.

The term "EG-VEGF variant polypeptide" as defined in the specification at page 13 is any EG-VEGF having one more amino acid residues are added, or deleted, tat the N- and/or C-terminals as well as within one or more internal domains of SEQ ID NO: 2. The EB-VEGF variant polypeptide does not encompass the native EG-VEGF polypeptide sequence. EG-VEGF variant polypeptides are at least 10 amino acids in length (see page 14). The allelic variant of EG-VEGF will have at least about 80%, 85%, 90% or 95% identity from x to 105 of amino acid of SEQ ID NO: 2 (see page14).

The specification discloses only one isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human EG-VEGF for screening agonist or antagonist (page 54-56) and production of antibody that binds specifically to EG-VEGF (See page 65). The mature EG-VEGF has the amino acid residues 20 to 105 of SEQ ID NO: 2. The specification further discloses that EG-VEGF is expressed in the endocrine tissues such as the stroma cell and granulose cells in the ovary, the Leydig cell in the testis, the adrenal gland and the placenta. The EG-VEGF is mitogenic and chemo attractant for specific endothelial cells but not human aortic vascular smooth muscle cells, pericytes, fibroblast, human neonatal fibroblasts and karatinocytes. The angiogenic effect of EG-VEGF is tissue specific since EG-VEGF has no effect on rat corneal pocket assay. The specification further discloses that injection of Adenoviral vector carrying the human EG-VEGF cDNA or VEGF causes an increase in angiogenesis, large fluid-filled or hemorrhagic cystic formation in ovary (Fig. 19).

With the exception of the specific polypeptide mentioned above, there is insufficient written description about the structure associated with function of any and all polypeptide

comprising any amino acid sequence having at least about 80%, 85%, 90%, or 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2, or any and all polypeptide comprising an amino acid sequence having at least about 80%, 85%, 90%, or 95% identity to any portion of amino acid residues 20 to 105 of SEQ ID NO: 2 without the amino acid sequence. This is because the term "an amino acid sequence" is not limiting to amino acid residues 20 to 105 of SEQ ID NO: 2. Further, the disclosure fails to adequately describe which amino acids within the full-length sequence of SEQ ID NO: 2 to be substituted, deleted, added and/or combination thereof and still maintains its structure and function. The term "comprising", "comprises" or 'having" is open-ended. It expands the fragment from amino acid residues 20, 21, 22... to 105 of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of disclosure about which amino acids to be added, hence the length of the polypeptide is not adequately described. The term "about" also expands the identity to include additional percentages to either or both ends of 80%, 85%, 90% and 95%. There is inadequate written description about the structure associated with function of any polypeptide, any polypeptide such as any allelic variant of EG-VEGF without the amino acid sequence.

Given the specification discloses only human EG-VEGF comprising the amino acid sequence of SEQ ID NO: 2, the genus of EG-VEGF and "allelic variant" of EG-VEGF without the amino acid sequence are not adequately described.

The specification discloses only human EG-VEGF comprising SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of allelic variants to describe the genus for the claimed polypeptide. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/12/06 have been fully considered but are not found persuasive.

Applicants' position is that the amended claims are directed to a genus of polypeptides having at least 80% identity to amino acid residues 20-105 of SEQ ID NO: 2 and ACE cell proliferation activity. As discussed above, Brenner et al. discloses that sequence comparison

methods are adequate and useful for predicting shared function. As discussed above, the specification describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions; how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding algorithm; how to use DNA comprising the coding sequence of mature EG-VEGF, for example, as a probe to screen for homologous DNAS encoding naturally occurring variants of EG-VEGF; how to express EG-VEGF in cells; how to make antibodies that specifically bind EG-VEGF; and how to screen EG-VEGF for ACE cell proliferation activity. In addition, angiogenic factors, such as VEGF, were known to exist in families having high amino acid sequence identity. See, for example, Table 2 below. Therefore, one of skill in the art would have reasonably expected EG-VEGF, an angiogenic factor, to be a member of a protein family (including variants and homolog) having high amino acid sequence identity. The post filing publications of Lecouter et al., Masuda et al., and Kisliouk et al. confirm that SEQ ID NO:2 is a member of a family having high amino acid sequence identity. Table 1 shows that mature mouse, rat, and bovine EG-VEGF have at least 88% amino acid sequence identity with mature human EG-VEGF (residues 20-105 of SEQ ID NO:2). The Office Action alleges the claims lack written description as the term "comprising" expands the polypeptide sequence of amino acids 20-105 to include additional amino acids at the N- terminal and/or C-terminal of the polypeptide. Applicants respectfully do not agree. As discussed above, the specification discloses that EG-VEGF can have a signal sequence. The specification also discloses chimeric molecules comprising EG-VEGF. For example, EG-VEGF can be fused with an epitope tag, such as a poly-his tag, to facilitate detection or purification or fused with an immunoglobulin to form a bivalent chimeric molecule (page 35, line 13 to page 36, line 11, and Example 4). Methods for making chimeric molecules are well known. Applicants therefore submit the claims satisfy the written description requirement.

In response, it appears that applicant's argument is for enablement. The examiner's rejection is for written description. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification as filed discloses only one isolated EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human EG-VEGF for screening agonist or antagonist (page 54-56) and production of antibody that binds specifically to EG-VEGF (See page 65).

The specification as filed does not disclose any polypeptide that comprise the full-length sequence having at least about 80%, 85%, 90%, 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or any polypeptide that comprise an amino acid sequence having at least about 80%, 85%, 90%, 95% identity to any portion from amino acid residues 20 to 105 of SEQ ID NO: 2 without the amino acid sequence. The specification as filed neither disclose any allelic variant sequences, nor does it demonstrate that allelic variant of EG-VEGF promotes proliferation of adrenal cortex-derived capillary endothelial cells. Therefore, the term "allelic variant" does not meet the written description provision of 35 U.S.C. 112, first paragraph. The skilled artisan can envision neither all the contemplated amino acid sequence possibilities of the "allelic variants", nor the function of proteins. Consequently, conception in either case cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived.

The specification discloses only human EG-VEGF comprising SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of allelic variants to describe the genus for the claimed polypeptide. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

With respect to the argument that the specification discloses EG-VEGF can have a signal sequence, full-length EG-VEGF (SEQ ID NO: 2), or chimeric molecule comprising EG-VEGF, such as EG-VEGF can be fused with epitope tag, poly-his tag, amending the claims to recite a chimeric protein comprising the amino acid residues 20 to 105 of SEQ ID NO: 2 fused to a heterologous polypeptide selected from the group consisting of the ones recited at page 35 lines 24-30 would obviate this rejection.

8. Claims 6 8, and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner

Technology Center 1600

March 31, 2006

CHRISTINA CHAN
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